Please add the following new claims:

37 CFR 1.663

--40. The replication defective recombinant adenovirus according to claim 17, wherein the sequence permitting expression of the heterologous DNA sequence is a promoter.

41. The replication defective recombinant adenovirus of claim 40, wherein the promoter is selected from the group consisting of an E1A promoter, a MLP promoter, a CMV promoter, and an RSV promoter.--

## REMARKS

Claims 1-3, 6 and 9-41 are pending in this application. Claims 1-3, 6, and 9-39 have been amended in order to more particularly point out and distinctly claim that which Applicants regard as their invention. Support for the amended claims, and for new claims 40 and 41, can be found in the original claims, and in the Specification as follows:

| | |
|---|---|
| Claims 1-3, 6, 9-19, 28, 29, 31, 32, and 34-41: | page 4, lines 6-15 |
| Claims 2 and 11: | page 3, line 34 to page 10, line 25 and page 11, lines 6-10 |
| Claim 14: | page 7, line 35 to page 8, line 5 and line 19 |
| Claims 15 and 16: | page 1, lines 13-16; page 4, line 21; and page 6, line 29 to page 8, line 15 |
| Claims 17, 40 and 41: | page 8, lines 16-36 |
| Claim 18: | page 9, lines 1-7 |
| Claims 21, 26, and 33: | page 20, lines 25-27 |
| Claim 27: | page 15, lines 13-18 and Example 4 |
| Claim 34: | page 19, line 30 to page 20, line 9 |
| Claim 35: | page 17, lines 19-21 and page 18, |

lines 13-26

Claim 36: page 9, line 8 to page 10, line 23

Claim 39: page 4, lines 6-15, page 9, line 8 to page 10, line 23

No new matter has been added.

**Summary of the Examiner's Office Action**

The Office action dated April 28, 1998 contains the following:

(1) Objection to the claims 2, 3, 6, 9-30, 32, 33, and 37-39;
(2) Rejection of Claims 21, 26, and 33-35 Under Section 112, First Paragraph;
(3) Rejection of Claims 13-27 and 33-39 Under Section 112, Second Paragraph;
(4) Rejection of Claims 1, 3, 6, 9, 10, 12-14, 17-19, 23, 27-32, 36, and 37 Under Section 102(e); and
(5) Rejection of Claims 1, 3, 9, 12, 14-17, 19, 23, 27, 28, 30, and 31 Under Section 103(a).

Each of the issues raised by the Examiner are discussed below. Applicants believe that the foregoing amendment and the following remarks respond completely to the objections and rejections. Applicants further believe the claims are in condition for allowance.

**(1) Objection to the claims**

The Examiner has objected to the language of claims 2, 3, 6, 9-30, 32, 33, and 37-39. In response, Applicants have amended the claims essentially according to the Examiner's suggestions.

Applicants note that the Examiner has indicated on page 12 of the Office Action that claims 2 and 11 would be allowable if rewritten in independent form to include all of the limitations of base claim 1. Applicants have amended Claims 2 and 11 accordingly, and respectfully submit that these claims are, therefore, allowable.

**(2) Rejection of Claims 21, 26, and 33-35 Under Section 112, First Paragraph**

Claims 21, 26, and 33-35 stand rejected under 35 USC § 112, first paragraph. Applicants respectfully traverse this rejection. The claims have been amended essentially according to the Examiner's suggestions, and to more clearly define the metes and bounds of their invention. Therefore, this rejection should be withdrawn.

Applicants note that the Examiner has indicated on page 12 of the Office Action that claims 20-22, 24-26, and 33 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. § 112. The present amendment to claims 21, 26, and 33 obviates the Examiner's rejection under 35 U.S.C. § 112, first paragraph. Therefore, Applicants respectfully submit that these claims are allowable.

**(3) Rejection of Claims 13-27 and 33-39 Under Section 112, Second Paragraph**

Claims 13-27 and 33-39 stand rejected under 35 USC § 112, second paragraph. Applicants respectfully traverse this rejection. The claims have been amended in accordance with the Examiner's suggestion, and in order to more particularly point out and distinctly claim what Applicants regard as their invention. In addition, new claims 40 and 41 have been added in order to further define the invention of claim 17. No new matter has been added.

> Specifically with respect to claims 17 and 18, the Examiner states:
>
> it is unclear if the "promoter" and "signal sequence" have any relationship with the genes present in the heterologous DNA sequence, other than proximity. In the case of a promoter, if the promoter is operationally linked to the gene, then claim 17 would not further limit claim 12, since a gene is understood in the art to comprise a promoter and often also comprises transcriptional regulatory elements

(Office Action at page 7). Applicants respectfully point out that claim 1, from which claims 17 and 18 ultimately depend, defines a replication defective recombinant adenovirus comprising ITR sequences, an encapsulation sequence, and a heterologous DNA sequence. According to Applicants' Specification, the heterologous DNA sequence may, or may not, comprise a promoter sequence. Applicants direct the Examiner's attention to page 8 (lines 33-36) of the Specification, which discloses that a heterologous DNA sequence may not contain intrinsic expression control sequences. Under these circumstances the heterologous DNA sequence may be inserted into a region of the adenovirus genome downstream of an intrinsic adenoviral transcriptional regulatory sequence. This disclosure clearly indicates that the heterologous DNA sequence need not comprise its own sequences enabling expression in an infected target cell. Therefore, claim 17, as amended, properly defines a replication defective recombinant adenovirus comprising a heterologous DNA sequence, wherein the heterologous DNA sequence further comprises sequences which permit expression in an infected cell. New claims 40 and 41 further limit claim 17. Applicants respectfully submit that amended claim 17, and new claims 40 and 41, are definite and clear and meet the requirements of 35 U.S.C. § 112, second paragraph.

Similarly, claim 18 has been amended to indicate that the heterologous DNA sequence further comprises a signal sequence, which would direct an expression product into a secretory pathway of a target cell. Applicants respectfully submit that claim 18 is definite and clear and meet the requirements of 35 U.S.C. § 112, second paragraph.

Based upon the present amendment and the above remarks, Applicants submit respectfully that the Examiner's rejection of claims 13-27 and 33-39 are obviated in part and overcome in part. Applicants submit that claims 13-27 and 33-39, as amended, are definite and clear, and meet the requirements of 35 USC § 112, second paragraph. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Applicants again note that the Examiner has indicated on page 12 of the Office Action that claims 20-22, 24-26, and 33 would allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. § 112. The present amendment obviates the rejection of claims 20-22, 24-26, and 33 under 35 U.S.C. § 112, second paragraph. Therefore, these claims are allowable.

**(4) Rejection of Claims 1, 3, 6, 9, 10, 12-14, 17-19, 23, 27-32, 36, and 37 under 35 U.S.C. § 102(e)**

Claims 1, 3, 6, 9, 10, 12-14, 17-19, 23, 27-32, 36, and 37 stand rejected under 35 U.S.C. § 102(e) as anticipated by Gregory *et al.* Applicants respectfully traverse this rejection. To anticipate a claim, a reference must teach every element of the claim.

> A claim is anticipated only if each an every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.

Verdegaal Bros. v. Union Oil Company of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). In this case, Gregory et al. fail to teach the invention defined by any of claims 1, 3, 6, 9, 10, 12-14, 17-19, 23, 27-32, 36, and 37.

Discussion of Gregory et al.

Gregory et al. disclose adenovirus-based gene therapy vectors which comprise an adenovirus genome, in which the E1a and E1b regions have been deleted and replaced by genetic material of interest (e.g., DNA encoding the cystic fibrosis transmembrane regulator protein). These vectors retain

functional E2, E3, E4, and L1-L5 viral coding regions and are produced in human embryonic kidney 293 cells (see pages 4, 10, 11, 20, and 21, Example 7, and Figure 14). Gregory et al. teach that the 293 cells are immortalized with sheared fragments of the human Ad5 DNA, and express adenovirus early region 1 gene products (see page 21). Gregory et al. do not teach that the cells comprise a complementing gene under the control of an inducible promoter.

Gregory et al. also disclose a pseudo-adenovirus (PAV) which comprises adenovirus ITR sequences, minimal adenoviral 5' sequences necessary for helper virus dependent replication and packaging of the PAV, and genetic material of interest (see pages 4 and 12, Example 11, and Figure 16). The PAV vectors may also comprise the L5 region and the E4 ORF6 or E4 ORF3 from the E4 promoter, wherein all other E4 open reading frames are deleted (see pages 4, 12, and 13, Example 12, and Figure 17). Optionally, these PAV vectors may also include deletions in the E1 and/or E3 regions (see page 4). Gregory et al. teach the production of the E4 ORF6 expressing PAV vectors in human 293 cells (see page 45).

The PAV vectors require a helper virus for replication and packaging. Gregory et al. teach that the helper virus will be the predominant species in any PAV preparation (see pages 43 and 44). Therefore, Gregory et al. teach that several approaches may be taken to increase the proportion of PAV in the resultant vector preparations, including development of a packaging 293 cell line which expresses pIX to be used in conjunction with an engineered helper virus (see pages 43 and 44). Gregory et al. do not teach that the 293/pIX cells comprise a complementing gene under the control of an inducible promoter.

Gregory et al. do not anticipate the claimed invention

In contrast to the disclosure of Gregory et al., the present invention is neither a first generation E1-deleted adenovirus nor a "pseudo-adenovirus" as defined within the reference (col. 4, lines 11-21). In particular, Applicants' claims define 1) replication defective recombinant adenoviruses comprising ITR sequences, an encapsulation sequence, and a heterologous DNA sequence,

wherein specific adenoviral genes have been rendered non-functional, 2) compositions comprising these adenoviruses, and 3) cell lines comprising adenoviral genes which complement a non-functional gene, wherein at least one of the complementing genes is under the control of an inducible promoter.

More specifically, independent claim 1 defines a replication defective recombinant adenovirus, wherein the adenoviral E1 genes, and either the E2 or E4 genes, but not both, have been rendered non-functional. Dependent claims 6, 9, and 10 further define adenoviruses having non-functional L1-L5 genes, E3 genes, or E3 and L5 genes, respectively. Clearly, neither the E1-deleted adenovirus nor the PAV of Gregory et al. anticipates the invention defined by claim 1, or the claims dependent thereon.

Independent claim 31 defines a replication defective recombinant adenovirus, wherein the adenoviral E3 and E4 genes have been rendered non-functional. Dependent claim 32 further comprises nonfunctional L1-L5 genes. Neither the E1-deleted adenovirus nor the PAV of Gregory et al. anticipates the invention defined by claims 31 and 32 of the present application.

Independent claim 36 defines a replication defective recombinant adenovirus, wherein the adenoviral E4 genes have been rendered non-functional by one or more modifications outside of the E4 coding region. Dependent claim 37 requires that the E4 genes have been rendered non-functional by deletion of all or part of the promoter region for E4 transcription. Gregory et al. neither teach nor suggest manipulation of E4 gene expression by modification outside of E4 coding region. Accordingly, Gregory et al. cannot possibly anticipate the invention of claim 36, or the claims dependent thereon.

Claims 19, 23, and 27 relate to cell lines comprising adenoviral genes integrated into their genome, and which are necessary to complement the replication defective recombinant adenoviruses of the invention. At least one of the complementing genes is under the control of an inducible promoter. Gregory et al. neither teach nor suggest controlling the expression of a complmenting gene with an inducible promoter. Accordingly, Gregory et al. cannot possibly anticipate the invention of claims 19, 23 and 27.

Claims 28-30 define compositions comprising the replication defective recombinant adenoviruses of the invention and a pharmaceutically acceptable carrier. For the reasons discussed above, neither the E1-deleted adenovirus nor the PAV of Gregory et al. anticipates the compositions defined by claims 28-30.

Summary

The legal test for anticipation under 35 U.S.C. § 102 requires that each and every element of the claimed invention be disclosed in a prior art reference in a manner sufficient to enable one skilled in the art to reduce the invention to practice, thus placing the public in possession of the invention. *See W.L. Gore Associates v. Garlock, Inc.*, 721 F.2d 1540, 1554, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); *In re Donohue*, 766 F.2d 531, 226 U.S.P.Q. 619 (Fed. Cir. 1985). Lacking any teaching of the claimed invention, Gregory *et al.* cannot possibly anticipate it.

Gregory *et al.* do not teach how to make or use the recombinant adenoviral vectors, cell lines and compositions of claims 1, 3, 6, 9, 10, 12-14, 17-19, 23, 27-32, 36, and 37. The reference provides no hint or suggestion of the invention, much less the express teaching of each and every element required to modify their disclosed adenovirus vectors or pseudo-adenovirus vectors and cell lines, to produce the vectors, cell lines and compositions of Applicants' invention. Accordingly, Applicants submit that this rejection is untenable, and should be withdrawn.

**(5) Rejection of Claims 1, 3, 9, 12, 14-17, 19, 23, 27, 28, 30, and 31 Under 35 U.S.C. § 103(a)**

Claims 1, 3, 9, 12, 14-17, 19, 23, 27, 28, 30, and 31 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Davis *et al.*, in view of Gregory *et al.* Applicants respectfully traverse this rejection, and submit that the combined

teachings of Davis *et al.* and Gregory *et al.* fail to suggest the claimed invention. Accordingly, these references fail to establish a *prima facie* case of obviousness. Therefore, Applicants request respectfully that the rejection be reconsidered and withdrawn.

Discussion of Davis et al.

Davis et al. has been previously cited by the Office and overcome (see Paper No. 7 and Paper No. 11). Davis et al. teach replication competent adenoviruses in an enteric-coated form, wherein the viruses have been engineered to contain genes coding for antigens produced by other disease-causing organisms (column 1). Davis et al. teach that upon release in the intestine, the viruses will reproduce in the gut wall, express the desired antigen, and induce antibody formation or cell mediated immunity to both the desired foreign antigen and the adenovirus.. Davis et al. disclose that these replication competent adenoviruses may be prepared in 293 cells, A549 cells, in diploid fibroblasts with helper virus, or in complementing cell lines.

Davis et al. neither teach nor suggest replication defective recombinant adenoviruses. Neither does the reference teach producer cells containing at least one complementing gene under the control of an inducible promoter. It follows that then that the reference cannot possibly teach or suggest the specific replication defective adenoviruses or cells defined by the present claims.

Gregory et al. fail to remedy the deficiencies of Davis et al.

Gregory et al., discussed above, is limited to first generation E1-deleted adenovirus and a "pseudo-adenovirus." However, the reference provides no hint or suggestion of the invention, or any teaching as to how to modify their disclosed adenovirus vectors, pseudo-adenovirus vectors or cell lines, to produce the vectors, cell lines and compositions claimed herein. Absent such a disclosure, Gregory et al. cannot possibly remedy the deficiencies of Davis et al.

Therefore, Applicants do not believe that a *prima facie* case of obviousness is established by the present combination of references. The recent decision of the Federal Circuit in *In re Rouffet*, 47 USPQ 1453 (Fed. Cir. 1998) sets forth the basis on which a combination of references may validly be cited against proposed claims. As the Court states at the bottom of page 1457

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the Examiner to show a motivation to combine the references that create the case of obviousness. In other words, the Examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

There appears to be no showing here. Specifically, there is no teaching or suggestion for modifying a replication defective recombinant adenovirus in the manner specifically claimed by Applicants. As Davis *et al.* are merely concerned with replication competent adenoviruses for vaccination purposes, it is not seen how this reference could not possibly teach or suggest the replication defective recombinant adenoviruses of Applicants' invention. Indeed, Davis *et al.* actually teach away from the present invention by requiring that their vectors be replication competent.

While Gregory *et al.* disclose first generation replication defective adenoviruses and PAVs, and teach that E4 deletions may be made, the reference provides no incentive to the skilled artisan to modify the adenoviral vector of Davis *et al.* to obtain the defective adenoviruses of Applicants' invention. Furthermore, Gregory *et al.* fail to suggest the specific functional and non-functional gene requirements within the replication defective recombinant adenoviruses of Applicants' invention. Absent such a disclosure, this rejection must be based on improper hindsight derived from Applicants' disclosure.

The Examiner cannot rely on hindsight to arrive at a determination of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). The Court of Appeals for the Federal Circuit has stated that "selective hindsight is no

more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the Applicant's disclosure" [*Interconnect Planning Corporation v. Fed.*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985)]. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988).

The present rejection fits squarely within the definition of improper determination of obviousness because the prior art contains no suggestion of the desirability of the modification made by Applicants in their claimed invention. Nothing in the references cited by the Examiner provides any indication of the advantages of the claimed invention as demonstrated in Specification. Indeed, the only suggestion to combine the references cited by the Examiner is found in the instant Specification. Thus, the Examiner has improperly relied on hindsight. Accordingly, Applicants request that this rejection be reconsidered and withdrawn.

In view of the foregoing amendments and remarks, Applicants submit that this application is in condition for allowance. Favorable reconsideration and an action passing this case to issue are therefore requested respectfully. If a telephone interview would be of assistance in advancing prosecution of this application, Applicant's attorney invites the Examiner to contact him at the number below.

Respectfully submitted,

Dated: 10-28-98

Ross J. Oehler
Attorney for Applicants
Registration No. 33,270

Rhône-Poulenc Rorer, Inc.
P.O. Box 5093, Mail Drop 3C43
Collegeville, PA 19426-0997
Telephone: (610) 454-3883
Telecopy (610) 454-3808